**Abstracts**

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**CATEPSIN C PROMOTES TUMOR GROWTH AND METASTASIS THROUGH ACTIVATING TNF-α/ MAPK (P38) PATHWAY IN HEPATOCELLULAR CARCINOMA**

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**Background** Although cathepsin C (CTSC), a multifunctional molecule, has been reported to maintain various malignant biological properties in several types of cancers, the potential function of CTSC in HCC remains obscure. We aimed to investigate the potential role of cathepsin C (CTSC) in the tumorigenesis of HCC.

**Methods** One hundred and twenty-two HCC specimens upon tissue microarrays were employed to analyze the correlation between CTSC expression and clinicopathological characteristics through immunohistochemistry staining. qRT-PCR, western blot assay, CCK-8 assay, colony formation, cell migration and invasion assays, xenograft mice model were adopted to validate what had been indicated by the bioinformatic web tools.

**Results** In our study, by the bioinformatic tools and tissue microarrays, CTSC was found upregulated in HCC compared with normal liver tissues, and its higher expression was correlated with poor prognosis of HCC patients. By gain-of-function and loss-of-function studies, we implicated that CTSC functioned as an oncogene to promote the proliferation, migration and invasion of HCC cells. Mechanistically, we revealed that CTSC was involved in several cancer-related signaling pathways by Gene Set Enrichment Analysis (GSEA), among which TNF-α/p38 pathway was verified to be activated by CTSC. Furthermore, we found that TNF-α could activate CTSC expression in a concentration-dependent manner. Ralmetinib, an oral MAPK (p38) inhibitor could inhibit CTSC expression. These indicated a potential positive feedback loop between CTSC and TNF-α/MAPK (p38) signaling.

**Conclusions** Taken together, CTSC plays an important role in the growth and metastasis of HCC and may be a promising therapeutic target upon HCC.

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**EVALUATION ON THE PROTECTION EFFECT OF THE VISMISO IN THE LIVER DAMAGE INDUCED BY PARACETAMOL IN MICE EXPERIMENT**

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**Background** This study was conducted to evaluate the hepatoprotective and antioxidant effects of Vismisco (extracted from Vigna radiata (L.) Wilczek, Smilax glabra roxb, Scoparia dulcis L.) in the liver damage induced by paracetamol in mice experiment.

**Aim** Study the hepatoprotective effect of Vismisco on the paracetamol-induced hepatotoxicity.

**Methods** Swiss albino mice weighing 25 ± 2 gram were divided into three groups of ten animals; Group 1: oral distilled water of 0.2 ml/10g; Group 2: oral distilled water and take paracetamol 400 mg/kg; Group 3: oral Silymarin at the dose of 140 mg/kg/day and take paracetamol 400 mg/kg; Group 4: oral Vismisco at the dose of 0.6g/kg/day and take paracetamol 400 mg/kg; Group 5: oral Vismisco at the dose of 1.8g/kg/day and take paracetamol 400 mg/kg. Swiss albino mice were oral with a single dose of 400mg/kg paracetamol to induce toxicity, while Vismisco administered in a dose of 0.6g/kg/day and 1.8g/kg/day. Animals were treated daily by the oral route of administration one a day in the morning for successive 8 days and observed once daily. On the 8th day after taking 2 hours of reagent, mice were given oral paracetamol dose of 400 mg/kg. Mice were sacrificed 48h after paracetamol oral to determine serum ALT, AST hepatic content of malonyl dialdehyde (MDA) and liver histopathology.

**Results** The 8 days pretreatment of Vismisco at the oral dose of 0.6g/kg and 1.8g/kg increases the detoxified function of the liver and reduces the increasing level of ALT, AST ALT reduces the increasing level of hepatic MDA, reduced the inflammation, hepatocellular necrosis which was induced by paracetamol.

**Conclusions** Vismisco has the hepatoprotective effect from oxidative damages induced by reducing the generation of free radicals in the metabolic process of paracetamol, interrupt the lipid peroxidation of cellular membranes.

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**METABOLIC-IMMUNOREGULATORY ROLE OF MTOR SIGNALING IN NAFLD-ASSOCIATED HEPATOCELLULAR CARCINOMA**

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**Background and objective** Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer deaths worldwide. Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of disorders from simple steatosis to non-alcoholic steatohepatitis (NASH). Driven by the epidemics of obesity and diabetes, it is anticipated that NAFLD will become the most important cause of HCC. Activation of mammalian target of rapamycin (mTOR) pathway in NAFLD has been shown to promote deregulated lipid/glucose metabolism, immunosuppression and tumorigenesis.

**Methods** To fully decipher the anti-immune surveillance functions of mTOR pathway in NAFLD-associated HCC, we performed immune cell profiling and signaling characterization in a high-fat high-carbohydrate diet (HFFC)-induced obesity and NASH murine model.

**Results** We uncovered activation of mTORC1 signaling cascade and specific reduction in cytolytic natural killer T (NKT) cells, which subsequently enhanced tumor growth of orthotopically-implanted HCC tumor cells. Notably, treatment of the mTORC1/C2 dual kinase inhibitor vistusertib (AZD2014), currently undergone phase II/II clinical trials, not only abrogated mTORC1/SREBP2 signaling and cholesterol levels, but also depressed the cytolytic NKT cells in blood and liver leading to reduced tumorigenicity. Furthermore, NKT cells inactivation by a specific antibody targeting the CD1d receptor abolished anti-tumor effects of vistusertib.

**Conclusions** Collectively, this study elucidates the metabolic-immunosuppressive role of mTOR signaling in NAFLD-associated HCC and provides insights into the development of...